

Applicants respectfully traverse these grounds of rejection since the amended claims are believed to properly define the invention. Claim 10 has been amended to be directed to the treatment of acromegalia, hypophyseal adenomas and endocrinic gastrointestinal tumors, see claim 10. Therefore, this is believed to be clear to treat specific conditions. Claim 11 has been amended to provide basis for R_a and R_{2b} and to provide proper antecedent basis for the various terms. With respect to R'_2 , this has been changed to R'_1 and the variable R_{2b} , this has been corrected. Claim 13 is now dependent upon claim 11 and the missing element \bar{Y} has been supplied therein. Therefore, these grounds of rejection are obviated.

Claims 3, 4, 9 and 10 were rejected under 35 USC 112, first paragraph, as not being based upon an enabling disclosure in view of the expression "blocking of somatostatin receptors".

Applicants respectfully traverse these grounds of rejection since the present amendment changes the claims to read on the treatment of acromegalia, hypophyseal adenomas and endocrinic gastroenteropancreatic tumors which is supported by the specification in lines 14 to 16 of page 2. Therefore, it is believed that the claims are based upon an enabling disclosure.

In order to further substantiate this, Applicants are submitting herewith a declaration by Dr. Thurieau who conducted the various tests on the somatostatin receptors and the results in the Annex show that 66 compounds of the application are


clearly effective for the treatment of somatostatin receptors which are effective in treating the specific diseases set forth in claim 10 and the claims dependent thereon. Therefore, it is deemed that the specification is enabling for the present claims and withdrawal of this ground of rejection is requested.

With respect to the 35 USC 102 anticipation rejection labelled No. 4 of the first office action, this has been obviated by the correction of claim 11 with respect to R₁ being parachloro. Therefore, withdrawal of this ground of rejection is requested.

With respect to the 35 USC 103 rejection of the compounds of claims 3 to 5 and 9 to 11 over the Tahara et al reference, this does not teach any of Applicants' specific compounds and they are clearly excluded within the scope of the compound claims and the presently claimed compounds differ from the compounds of the Tahara et al reference in that they possess activity to treat illnesses set forth in the claims which the prior art compounds do not effect. Therefore, it is not merely a discovery of an additional property but, rather, a discovery of a new property not possessed by the prior art compounds. Therefore, this ground of rejection should be obviated.

In view of the amendments to the claims and the above remarks, it is believed that the claims clearly point out Applicants' patentable contribution and favorable reconsideration of the application is requested.

Respectfully submitted,
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CAM:ds
Enclosures

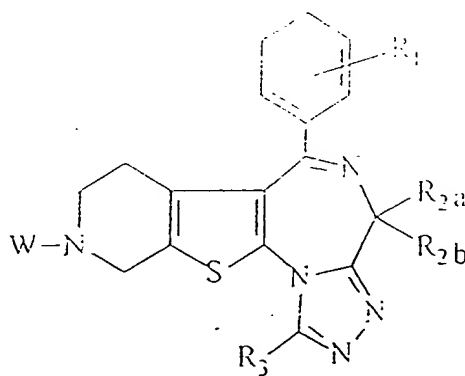


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MARKED UP VERSION OF CLAIMS SHOWING CHANGES MADE

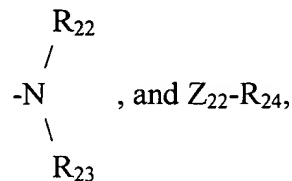
Claim 9 (twice amended) A composition for [blocking somatostatin receptors] treating acromegalia, hypophyseal adenomas and endocrinic gastroenteropancreatic tumors comprising an amount of a compound as defined in claim 10 sufficient to [block somatostatin receptors] treat acromegalia, hypophyseal adenomas and endocrinic gastroenteropancreatic tumors and an insert pharmaceutical carrier.

Claim 10 (twice amended) A method for [blocking somatostatin receptors] treating acromegalia, hypophyseal adenomas and endocrinic gastroenteropancreatic tumors in warm-blooded animals comprising administering to warm-blooded animals in need thereof an effective amount of a compound selected from the group consisting of a compound of the formula



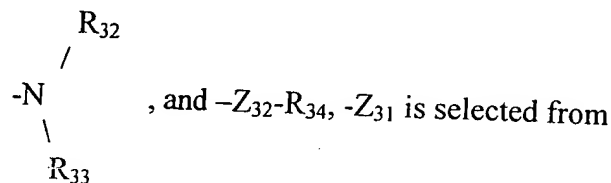
wherein W is hydrogen or R-X-C(Y)-, R is unsubstituted or substituted aryl or heteroaryl with at least one substituent selected from the group consisting of lower alkyl, lower

lower alkoxy, lower alkylthio, lower alkoxycarbonyl, lower alkylsulfonyl, halogen, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OH}$, $-\text{NO}_2$, $-\text{DN}$, aryl, aryloxy, cycloalkyl and heterocycloalkyl, X is $-(\text{CH}_2)_n-\text{Z}$, Z is selected from the group consisting of a covalent bond, $-\text{NH}-$, $-\text{O}-$ and $-\text{S}-$, n is 0, 1 or 2, Y is oxygen or sulfur, R_1 is selected from the group consisting of hydrogen, $-\text{OH}$, halogen, lower alkyl and lower alkoxy, the alkyl and alkoxy being unsubstituted or substituted with at least one member of the group consisting of $-\text{CF}_3$, lower alkoxy, $-\text{NH}_2$ and mono- and di-lower alkylamino, R_{2a} and R_{2b} are individually selected from the group consisting of hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl and $-\text{Z}_{21}-\text{R}_{21}$, the substituents being at least one member of the group consisting of halogen,



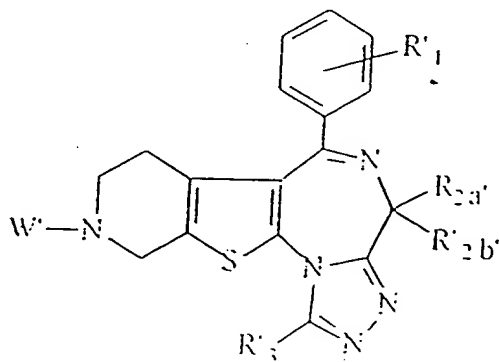
R_{22} and R_{23} are individually selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, lower alkoxycarbonyl, aryloxycarbonyl, alkylcarbonyl, arylcarbonyl and cycloalkylcarbonyl, Z_{21} and Z_{22} are individually selected from the group consisting of oxygen, sulfur, $-\text{CO}-$ and $-\text{O}-\text{CO}$, R_{24} is selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, alkylsulfonyl, cycloalkylsulfonyl, and arylsulfonyl, R_{21} is selected from the group consisting of hydrogen, lower alkyl, aryl and aralkyl, R_3 is selected from the group consisting of hydrogen, halogen, $-\text{NO}_2$, $-\text{CN}$, unsubstituted or substituted alkyl of 1 to 10 carbon atoms, unsubstituted or substituted lower alkenyl, unsubstituted or

substituted lower alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, unsubstituted or substituted aryl, unsubstituted or substituted aralkyl, unsubstituted or substituted lower aryloxalkyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroarylalkyl and $-Z_{31}R_{31}$, the substituents being selected from the group consisting of halogen, aryl



the group consisting of $-O-$, $-C(O)-$, $-OC(O)-$ and $-S-$, R_{31} is selected from the group consisting of hydrogen, lower alkyl, aryl and lower aralkyl, R_{32} and R_{33} are individually selected from the group consisting of hydrogen, lower alkyl, aralkyl and alkylcarbonyl or together with the nitrogen form a heterocycloalkyl, Z_{32} is selected from the group consisting of oxygen, sulfur, $-C(O)-$, $-S(O)-$, $-O-CO-$ and $-SO_2$, R_{34} is selected from the group consisting of hydrogen, lower alkyl, aryl and lower aralkyl and its non-toxic, pharmaceutically acceptable salts sufficient to treat [somatostatin receptors] said conditions.

Claim 11 (twice amended) A compound of the formula



II

wherein W' is hydrogen or $-C(Y')-X'-R'$, R' is selected from the group consisting of phenyl, naphthyl, indolyl and pyridyl, all unsubstituted or substituted with at least one member of the group consisting of methyl, ethyl, propyl, isopropyl, butyl, tert.-butyl, methoxy, ethoxy, methylthio, ethylthio, methoxycarbonyl, ethoxycarbonyl, methylsulfonyl, ethylsulfonyl, chlorine, fluorine, bromine, trifluoromethyl, trifluoromethoxy, -OH, -NO₂-, -CN, phenyl, phenoxy and morpholino, X' is selected from the group consisting of $-CH_2-$, $-CH_2-CH_2-$, $-CH_2NH-$, -NH-, -O-, -S- and a covalent bond, Y' is oxygen or sulfur, R'₁ is at least one member of the group consisting of hydrogen, chlorine, methyl and methoxy, [R'_{2a}] R_{2a}' and [R'_{2b}] R_{2b}' are individually hydrogen or methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, methoxyethyl, ethoxyethyl, dimethylaminoethyl, cyclohexylmethyl, phenyl, diphenyl, benzyl unsubstituted or substituted with -OH or methoxy, phenethyl, naphthylmethyl and indolylmethyl excluding the compounds of Formula II wherein a) W' is hydrogen, R'₁ is o-chlorine, [R'_{2a}] R_{2a}' is hydrogen, [R'_{2b}] R_{2b}' R_{2b}' is hydrogen or methyl and R'₃ is methyl and b) wherein W' is $-C(Y')-X'-R'$ and i) X' is -NH-, Y' is oxygen, R'₁ is o-chlorine, [R'_{2a}] R_{2a}' and [R'_{2b}] R_{2b}' R_{2b} are hydrogen, R'₃ is methyl and R' is selected from the group consisting of 4-tert.butyl-phenyl, 4-trifluoromethyl-phenyl, 4-hydroxy-phenyl, 4-methoxy-phenyl, 3,4,5-trimethoxy-phenyl, 2,3-dichloro-phenyl, 2,4-difluoro-phenyl, 4-phenoxy-phenyl, pyridinyl and cyanophenyl or ii) X' is -NH-, Y' is sulfur, R'₁ is o-chloro, [R'_{2a}] R_{2a}' and [R'_{2b}] R_{2b}' R_{2b} are hydrogen, R'₃ is methyl and R' is selected from the group consisting of 4-hydroxy-phenyl, 4-tert.butyl-phenyl, 2,4-ditert.butyl-

phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 4-methoxy-phenyl, 3,4,5-trimethoxy-phenyl, 4-fluoro-phenyl and 4-methylsulfonyl-phenyl or iii) X' is -CH₂-NH-, Y is oxygen, R'₁ is o-chlorine, [R'_{2a}] R_{2a}' and [R'_{2b}] R_{2b}' are hydrogen, R'₃ is methyl and R' is phenyl, or iiiii) X' is oxygen, Y' is oxygen, R'₁ is o-chlorine, [R'_{2a}] R_{2a}' and [R'_{2b}] R_{2b}' are hydrogen, R'₃ is methyl and R' is pyridyl or cyanophenyl or iiiiii) X' is CH₂, Y is oxygen R'₁ is O-chlorine and [R'_{2a}] R_{2a}' and [R'_{2b}] R_{2b}' are hydrogen, R'₃ is methyl and R' is phenyl or 4-fluoro-phenyl, iiiiii) X' is -CH₂-CH₂-, Y' is oxygen, [R'₂] R₁' is o-chlorine, [R'_{2a}] R_{2a}' and [R'_{2b}] R_{2b}' are hydrogen, R'₃ is methyl and R' is phenyl or iiiiii) X' is a covalent bond and Y' is oxygen.

Claim 13 (amended) A compound of claim [5] 11 wherein W' is R'-X'-C(Y')- and the substituents R', X', Y', R'₁, R_{2a}, R_{2b} and R'₃ are respectively selected from the group consisting of:

- 2-F₃C-Ph ; CH₂ ; O ; 2-Cl ; H ; H ; Me ;
- 2-F₃C-Ph ; CH₂ ; S ; 2-Cl ; H ; H ; Me ;
- 2-F₃C-Ph ; NH ; O ; 2-Cl ; H ; H ; Me ;
- 2-F₃C-Ph ; CH₂NH ; S ; 2-Cl ; H ; H ; Me ;
- Ph ; O ; O ; 2-Cl ; H ; H ; Me ;
- 2-F₃C-Ph ; NH ; S ; 2-Cl ; Me ; H ; Me ;
- 2-F₃C-Ph ; NH ; S ; 2-Cl ; H ; H ; Bz ;
- 3-F₃C-Ph ; NH ; O ; 2-Cl ; H ; H ; Me ;
- 4-F₃C-Ph ; NH ; O ; 2-Cl ; H ; H ; Me ;
- 2-isoPr-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-NC-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-F₃C-Ph ; NH ; S ; 2-Cl ; H ; H ; Et ;
- 2-F₃C-Ph ; NH ; S ; 2-Cl ; H ; H ; H ;
- 2-terBu-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 1-naphthyl ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-Ph-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-F₃CO-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;

- 2-Cl-Ph; NH; S; 2-Cl; H; H; Me;
- 2-F-Ph; NH; S; 2-Cl; H; H; Me;
- 2-Et-Ph; NH; S; 2-Cl; H; H; Me;
- 2-PhO-Ph; NH; S; 2-Cl; H; H; Me;
- 2-Pr-Ph; NH; S; 2-Cl; H; H; Me;
- 2-EtO-Ph; NH; S; 2-Cl; H; H; Me;
- Ph; NH; S; 2-Cl; H; H; Me;
- 2-Br-Ph; NH; S; 2-Cl; H; H; Me;
- 2-EtOC(O)-Ph; NH; S; 2-Cl; H; H; Me;
- 2-MeS-Ph; NH; S; 2-Cl; H; H; Me;
- 2-morpholino-Ph; NH; S; 2-Cl; H; H; Me;

- 2-NO₂-Ph; NH; S; 2-Cl; H; H; Me;
- 2,6-isoPr-Ph; NH; S; 2-Cl; H; H; Me;
- 2,6-Me-Ph; NH; S; 2-Cl; H; H; Me;
- 2,5-(MeO)-Ph; NH; O; 2-Cl; H; H; Me;
- 2-MeO-5-Cl-Ph; NH; S; 2-Cl; H; H; Me;
- 2,4-(MeO)-Ph; NH; S; 2-Cl; H; H; Me;
- 2-Cl-5-F₃C-Ph; NH; S; 2-Cl; H; H; Me;
- 2-Me-5-Cl-Ph; NH; S; 2-Cl; H; H; Me;
- 2,3-Cl-Ph; NH; S; 2-Cl; H; H; Me;
- 2,5-Me-Ph; NH; S; 2-Cl; H; H; Me;
- 2,5-Cl-Ph; NH; S; 2-Cl; H; H; Me;
- 2-Cl-4-Me-Ph; NH; S; 2-Cl; H; H; Me;
- 2-Me-3-Cl-Ph; NH; S; 2-Cl; H; H; Me;
- 2-Me-5-F-Ph; NH; S; 2-Cl; H; H; Me;
- 2,3-Me-Ph; NH; S; 2-Cl; H; H; Me;
- 2-F₃C-4-Br-Ph; NH; S; 2-Cl; H; H; Me;
- 2-NO₂-4-MeO-Ph; NH; S; 2-Cl; H; H; Me;
- 2-NO₂-4-Me-Ph; NH; S; 2-Cl; H; H; Me;
- 2-MeO-4-NO₂-Ph; NH; S; 2-Cl; H; H; Me;
- 2,5-Br-Ph; NH; S; 2-Cl; H; H; Me;
- 2-MeO-5-NO₂-Ph; NH; S; 2-Cl; H; H; Me;
- 2-Cl-4-NO₂-Ph; NH; S; 2-Cl; H; H; Me;
- 2-Cl-5-NO₂-Ph; NH; S; 2-Cl; H; H; Me;
- 2-F₃C-Ph; NH; S; 2-Cl; H; H; Pr;

- 2-F₃C-Ph ; NH ; S ; 2-Cl ; H ; H ; Bu ;
- 3-Ph-6-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-F₃C-Ph ; NH ; S ; H ; H ; H ; Me ;
- 2-F₃C-Ph ; NH ; S ; 2-Cl ; H ; H ; Ph ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; Pr ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; Bu ;
- 2-NO₂-4-F₃C-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-MeSO₂-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-F₃C-4-Cl-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 4-Cl ; H ; H ; Bz ;
- 2-F₃C-Ph ; NH ; S ; 4-Cl ; H ; H ; Me ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; pentyl ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; hexyl ;
- 3,5-F₃C-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 3-Cl ; H ; H ; Bz ;
- 2-NO₂-4-F-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-4-NC-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; 1-naphthyl-methyl ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; 3-indolyl-methyl ;
- 2-MeS-5-F₃C-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 3-Cl ; H ; H ; Me ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-4-HO-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-5-Cl-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-5-Me-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-4-EtO-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; 4-MeO-Bz ;
- 2-NO₂-4-Cl-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-Br-4-Me-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; 4-HO-Bz ;
- 2-F₃C-4-NO₂-Ph ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; H ; H ; H ; Bz ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; Ph-C₂H₄ ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; EtOC₂H₄ ;
- 3-NO₂-2-pyridyl ; NH ; S ; 2-Cl ; H ; H ; Me ;
- 4-MeO-Ph ; CH₂ ; O ; 2-Cl ; H ; H ; Me ;

- 2-indolyl ; - ; O ; 2-Cl ; H ; H ; Me ;
- 3-indolyl ; CH₂ ; O ; 2-Cl ; H ; H ; Me ;
- 4-HO-Ph ; C₂H₄ ; O ; 2-Cl ; H ; H ; Me ;
- 2-F₃C-Ph ; - ; O ; 2-Cl ; H ; H ; Me ;
- 4-HO-Ph ; CH₂ ; O ; 2-Cl ; H ; H ; Me ;
- 5-MeO-2-indolyl ; - ; O ; 2-Cl ; H ; H ; Me ;
- Ph ; - ; O ; 2-Cl ; H ; H ; Me ;
- Ph ; - ; S ; 2-Cl ; H ; H ; Me ;
- 5-MeO-2-indolyl ; - ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-Ph ; CH₂ ; O ; 2-Cl ; H ; H ; Me ;
- 2-F₃C-Ph ; CH₂ ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 4-Cl ; H ; H ; Me ;
- 2-NO₂-Ph ; CH₂ ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-MeO ; H ; H ; Bu ;

- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-MeO ; H ; H ; Bz ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Me ; H ; H ; Bu ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Me ; H ; H ; Bz ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; Ph-Ph ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; cyclohexyl methyl ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; (Me)₂NC₂H₄ ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; 3-HO-Bz ;
- 2-pyridyl ; NH ; S ; 2-Cl ; H ; H ; Me ;
- Ph ; S ; S ; 2-Cl ; H ; H ; Me ;
- Ph ; O ; S ; 2-Cl ; H ; H ; Me ;
- 2-NO₂-4-MeO-Ph ; NH ; S ; 2-Cl ; H ; H ; heptyl ;

and the compounds of formula II wherein W is hydrogen and substituents R'₁, R'_{2a}, R'_{2b} and R'₃ are respectively selected from the group consisting of:

- 2-Cl ; H ; H ; butyl ;
 - 2-Cl ; H ; H ; benzyl ;
 - 2-Cl ; H ; H ; H ;
 - 2-Cl ; H ; H ; ethyl ;
 - 2-Cl ; H ; H ; propyl ;
 - 2-Cl ; H ; H ; Ph ;
 - 2-Cl ; H ; H ; pentyl ;
 - 2-Cl ; H ; H ; hexyl ;
 - 2-Cl ; H ; H ; 4-HO-Bz ;
 - 2-Cl ; H ; H ; 4-MeO-Bz ;
 - 2-Cl ; H ; H ; 1-naphthyl-methyl ;
 - 2-Cl ; H ; H ; 3-indolyl-methyl ;
 - 2-Cl ; H ; H ; Ph-C₂H₄ ;
 - 2-Cl ; H ; H ; Ph-Ph ;
 - 2-Cl ; H ; H ; EtOC₂H₄ ;
-
- 2-Cl ; H ; H ; cyclohexylmethyl ;
 - 2-Cl ; H ; H ; 3-OH-Bz ;
 - 2-Cl ; H ; H ; (Me)₂NC₂H₄ ;
 - H ; H ; H ; Me ;
 - 4-Cl ; H ; H ; Bz ;
 - H ; H ; H ; Bz ;
 - 4-Cl ; H ; H ; Me ;
 - 3-Cl ; H ; H ; benzyl ;
 - 3-Cl ; H ; H ; Me ;
 - 2-Me ; H ; H ; butyl ;
-
- 2-Me ; H ; H ; benzyl ;
 - 2-MeO ; H ; H ; butyl ;
 - 2-Cl ; H ; H ; heptyl ;
 - 4-Cl ; H ; H ; hexyl ; and
 - 4-Cl ; H ; H ; pentyl.



60	234
61	1140
62	132
64	99
69	1500
70	581
72	289
79	180
81	83
83	130
86	205
91	143
92	54.5
95	473
96	250
97	84
98	1120
102	960
103	158
107	3730
108	710
111	520
112	556
113	1020
114	73.9
115	1650
116	577
117	195
121	90
134	606
135	268



136	631
138	76
141	79,5
144	163
146	5255

Examples 1-22 : Ki on sst4 ; examples 32-146 : Ki on sst2